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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/658,376	NILSSON, DAN	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,9-11,27 and 30-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *6,7,9-10,27 and 30-38* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 6, 7, 9-11, 27 and 30 as amended and new claims 31-38 (2/08/2007) are pending and under examination.

Deposit

The deposit requirement for strains *Lactococcus lactis subsp. lactis* DN221 (DSM 11034) and *Lactococcus lactis* subsp. *lactis* biovar *diacetylactis* DN227 (DSM 11040) have been met in the response papers filed 11/01/2005.

Claim Rejections - 35 USC § 112

New claims 35-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 35, 36 and 38 recite the Pfl defective bacteria (III) or (IV) that are mutants of the Pfl defective strains DN221 and DN 227 as claimed. The entities defined by these "mutant(s)"s (III) and (IV) is indefinite because it is unclear what "characteristics" of the parent strains DN221 and DN 227 are included into and/or excluded from the scope of the claimed subject matter as intended for the claimed invention. The claimed features from (i) to (v) relate to the Pfl defective strains that are exemplified by the strains DN 221 and DN 227. The as-filed specification describes a mutant obtained from DN 221 that will be a double mutant deficient for both Pfl and Ldh enzymatic activities (page 27). Thus, the claimed entity defined by the "mutant" (III) is drawn to a product distinct from the presently claimed invention that is a single mutant defective in Pfl activity. Therefore, the claims 35, 36 and 38 further extend rather than

limit the scope of the claimed invention. The pfl-defective mutant derived from the strain DN227 is not described in the as-filed specification and its features are uncertain as disclosed and as intended. Thus, the metes and bounds of the claimed "mutant(s)" can no be determined.

New matter

New claims 35-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Insertion of the limitation drawn to "a mutant obtained by mutation of strain DN227" in claim 35 and the mutant (IV) in claims 36 and 38 has no support in the as-filed specification.

The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited entity of a mutant IV obtained by mutation of strain DN227 that would show possession of the concept of the use of this mutated strain.

The pfl-defective mutant that is obtained by mutagenization of the strain DN227 is not described in the as-filed specification. The features for the presently claimed mutant IV are not described and, thus, unclear. The nature and effects of mutation as intended for mutant of DN 227 are not disclosed and, thus, cannot be determined. Given this lack of description of any representatives of the mutant IV encompassed by the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan

would recognize that applicant was in possession of the claimed invention, the entity of mutants derived from DN 227.

Thus, there is no sufficient support for the newly claimed entity of mutant IV. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of limitation drawn to "a mutant obtained by mutation of strain DN227" in claim 35 and to the mutant (IV) in claims 36 and 38 is considered to be the insertion of new matter for the above reasons.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6, 7 and 27 as amended remain rejected under 35 U.S.C. 102(a or b) as being anticipated by Takahashi et al. ("Oxygen sensitivity of sugar metabolism and interconversion of pyruvate formate lyase in intact cells of *Streptococcus mutans* and *Streptococcus sanguis*". Infection and Immunity. March 1987, Vol. 55, No. 3, pages 652-656) of by Yamamoto et al. ("Cloning and sequence analysis of the pfl gene encoding private formate lyases from *Streptococus mutans*. Infection and Immunity. February 1996, Vol. 64, No. 2, pages 358-391) as explained in the prior office action.

Claims are directed to a Pfl-defective mutant of lactic acid bacterium selected from the group of species belonging to *Streptococcus.* The claimed bacterium is characterized relatively to the parent or wild-type strain by at least one characteristics such as that it does not produce formate under anaerobic conditions, does not produce ethanol under anaerobic conditions, produced less of acid under anaerobic conditions, is characterized by production of acetolactate-derived metabolite(s), is characterized by capability to grow on M17 medium under aerobic conditions and/or has reduced growth on M17 medium under anaerobic conditions. The claimed bacterium is made by selection of mutants that does not growth on acetate-containing medium under anaerobic conditions. Some claims are further drawn to the strain capable of producing acetoin. Some claims are further drawn to a starter composition comprising the PFL defective lactic acid bacterium.

The cited references by Takahashi et al. and by Yamamoto et al. discloses Pfl-defective mutants of lactic acid bacteria belonging to *Streptococcus sp* and compositions therewith.

For example: see Takahashi et al. entire document including abstract and figures 1-2, wherein the reference teaches that exposure to oxygen result in inactivation of pfl and in possession of mutants with reversible and irreversible pfl. The mutants with inactivated pfl have at least one of the characteristics as required for the claimed mutant, for example: the oxygen inactivated mutants or the "aerated" cultures demonstrate "essentially no production of formate", "reduced production of ethanol and acetate", "reduced rate of acid production" under anaerobic conditions (figures 2 and 3).

For example: see Yamamoto et al. at page 385, col. 2, lines 7-8, wherein the reference explicitly reports an isolation of pfl-negative mutant of *Streptococus mutans*.

The claimed characteristics (i) through (v) are result of an inactivation of pfl or of a lack of pfl. Although characteristics of the parent or wild type strains of the referenced pfl mutants are not indicated or disclosed, the relative enhancement and/or relative differences of claimed features cannot be determined and they would not be meaningful unless some specific and particular strains are claimed. Although it is uncertain how the referenced bacteria have not been made or selected, they are the PFL-defective mutants and, thus, they are characterized by the same features that are required during selection method as encompassed by the claims. The PFL defective mutant in a culture medium is a starter composition within the meaning of the claims.

Thus, the presently claimed pfl defective mutant(s) and composition(s) therewith are anticipated by the cited references.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 7, 9-10, 27 and 30 as amended and new claims 31-34 remain/are rejected under 35 U.S.C. 102(a,b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hugenholtz (IDS reference; "Citrate metabolism in lactic bacteria". FEMS Microbiology Reviews 1993, 12, 165-178), Takahashi et al. ("Oxygen sensitivity of sugar metabolism and interconversion of pyruvate formate lyase in intact cells of *Streptococus mutans* and *Streptococcus sanguis*". Infection and Immunity. March 1987, Vol. 55, No. 3, pages 652-656), Yamamoto et al. ("Cloning and sequence analysis of the pfl gene encoding private formate lyases from *Streptococus mutans*. Infection and Immunity. February 1996, Vol. 64, No. 2, pages 358-391) in the light of evidence by the ATCC Catalogue as explained in the prior office action.

Claims are directed to a Pfl-defective mutant of lactic acid bacterium selected from the group of species belonging to *Streptococcus, Bifidobacterium, Pediococcus* and *Lactococcus* including *Lactococcus lactic subsp. lactis/diacetalicus.* The claimed bacterium is characterized relatively to the parent or wild-type strain by at least one characteristics such as that it does not produce formate under anaerobic conditions, does not produce ethanol under anaerobic conditions, is characterized by production of acetolactate-derived metabolite(s), is characterized by capability to grow on M17 medium under aerobic conditions and has reduced growth on M17 medium under anaerobic conditions. The claimed bacterium is made by selection of mutants that does not growth on acetate-containing medium under anaerobic conditions. Some claims are further drawn to the strain capable of producing acetoin. Some claims are further drawn to a starter composition comprising the PFL defective lactic acid bacterium.

The reference by Hugenholtz teaches that the group of lactic bacteria including homofermentative and heterofermentative lactic bacteria convert sugars to lactic acid via

intermediate pyruvate (page 171, col. 2, par. 3 and figure 1), that pfl in the lactic bacteria is responsible for production of formate, acetate and ethanol and that inactivation of the pfl activity in the mutants of the lactic bacteria result in disappearance of production of formate, acetate and ethanol (page 171, col. 2, par. 3).

In particular, the cited reference by Hugenholtz teaches that the pfl enzyme inactivation by oxygen and resulting changes in product formation are observed for *Lactococcus lactis* (page 171, col. 2, par. 3, lines 22-24 and fig. 2). The references by Takahashi et al. and by Yamamoto et al. teaches the same concept of pfl inactivation and resulting changes in product formation as observed for mutants of the *Streptococcus* species.

In view of the Fig. 1 teaching by Hugenholtz and in view of the fig. 2-3 teaching by Takahashi, the PFL "defective" mutants of lactic bacteria are and/or would be characterized by "essentially no production" of formate, acetate and ethanol and it they also would be characterized by production of acetolactate-derived metabolite(s) including acetoin as required for the claimed bacterium. Thus, the cited references by Hugenholtz et al., by Takahashi et al and/or by Yamamoto et al. appear to anticipate the claimed invention.

Although characteristics of the parent or wild type strains of the referenced PFL mutants are not indicated or disclosed, the relative enhancement and/or relative differences of claimed features cannot be determined and they would not be meaningful unless some specific and particular strains are claimed.

Although it is uncertain how the referenced bacteria have not been made or selected, they are the PFL-defective mutants and, thus, they are characterized by the same features that are required during selection method as encompassed by the claims.

The teaching of the cited references relate to the group of lactic bacteria as a whole including species belonging to *Streptococcus* and *Lactococcus* including *Lactococcus lactic subsp. lactis/diacetalicus*. Although some of the other species such as *Bifidobacterium* and *Pediococcus* are not explicitly disclosed by Hugenholtz et al., Takahashi et al and by Yamamoto et al., the bacterial species of lactic bacteria have been frequently cross-identified and reclassified between these genera and species (as demonstrated by ATCC catalogue, see pages 68, 199, 205, 264 and 346) and, thus, there is a reasonable believe that the pfl defective lactic bacteria of the cited references might be assigned to any and all of the presently claimed genera and/or species. Moreover, the reference by Hugenholtz teaches that lactic bacteria including homofermentative and heterofermentative lactic bacteria convert sugars to lactic acid via intermediate pyruvate (page 171, col. 2, par. 3 and figure 1), that pfl in the lactic bacteria is responsible for production of formate, acetate and ethanol and that inactivation of the pfl activity in the mutants of the lactic bacteria result in disappearance of production of formate, acetate and ethanol (page 171, col. 2, par. 3). Thus, regardless the specific taxonomic assignment of some particular species within the group of lactic bacteria, the pyruvate metabolism pathway and the end product resulting from the pfl inactivation are the same and/or similar for lactic bacteria as the whole group. Thus, the "pfl defective mutant" of the presently claimed species is an obvious variant the lactic bacteria disclosed by the cited references within the meaning of 35 U.S.C. 103(a).

Therefore, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed 2/08/2007 have been fully considered but they are not all found persuasive.

Claim 11, drawn to the specific applicants' isolates DN 221 and DN 227 deposited in DSM, is free from prior. The scope of new claims 35-37 as drawn the specific applicants' isolates DN 221 and DN 227 deposited in DSM, is also free from prior.

Claim 11 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

With regard to the claim rejections under 35 U.S.C. 102(a or b) as being anticipated by Takahashi et al. applicant argues that reference relates to a cell-free enzyme preparation but not to the bacterial cells or to bacterial strains (response page 6). This is not found true because Takahashi et al. clearly states that the Pfl activity in the intact cells of *S. mutants* lost was not recovered and, thus, it discloses a pfl deficient mutant (page 653, col. 2, par. 5, lines 17-18).

With regard to the claim rejections under 35 U.S.C. 102(a or b) as being anticipated by Yamamoto et al. applicant argues that the cited Pfl negative mutants are obtained by deletion of the entire Pfl gene unlike the applicants' Pfl defective bacteria that are obtained by spontaneous mutagenization that is most likely would be a point mutation of the promoter and/or coding sequences. This argument is not supported by any sequencing as disclosed in the as-filed specification and the exact nature of spontaneous mutation as disclosed cannot be determined. The product-by-process claims are not limited to the manipulations of the recited steps, only the

final structure implied by the steps. MPEP 2113. The final structure of the strain with inactivated Pfl gene as result of spontaneous mutation cannot be determined as disclosed and as argued and, thus, the cited mutants and the applicants' mutants cannot be reasonably distinguished.

With regard to the claim rejections under 35 U.S.C. 102/103 the arguments are directed to the idea that lactic acid metabolic pathways are distinct in the homofermentative lactic acid bacteria and in the heterofermentative lactic acid bacteria. However, as related to the pyruvate metabolism and the pfl inactivation the lactic bacteria are the same and/or similar since lactic bacteria convert sugars to lactic acid via pyruvate as intermediate product. Although the exact amounts of specific end products in homofermentative and heterofermentative lactic acid bacteria might be different, the inactivation of pfl in lactic acid bacteria result in the presently features including "essentially no production" of formate, acetate and ethanol as adequately taught and/or suggested by Hugenholtz et al. and Takahashi et al.

Applicant also argue that there is an art-recognized distinction between the claimed bacterial genera of *Streptococcus, Leuconostoc, Lactococcus*, *Bifidobacterium* and *Pediococcus* and, thus, the prior art relevant to the genus of *Streptococcus* and *Leuconostoc* would not be relevant to the biological function of *Lactococcus, Bifidobacterium* and *Pediococcus* . However, all claimed bacterial genera are regarded as lactic acid bacteria by applicant and the enzymatic pathway are manipulated as based on fermentative pathway of lactic bacteria as a whole group (page 8, last par.) rather than on the other art-recognized distinctive features such as, for example: morphology.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova
AU 1657
April 26, 2007

VERA AFREMOVA
PRIMARY EXAMINER